MAJOR ARTICLE

Sputum Culture Conversion With Moxifloxacin-Containing Regimens in the Treatment of Patients With Newly Diagnosed Sputum-Positive Pulmonary Tuberculosis in South India

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Background. Rapid sputum culture conversion at 2 months indicates the sterilizing capacity and potential of regimens to shorten duration of tuberculosis treatment. We compared results of sputum culture conversion by moxifloxacin and control regimens and identified factors affecting sputum culture positivity after 2 months of treatment.

Methods. Human immunodeficiency virus–uninfected adults with newly diagnosed smear-positive pulmonary tuberculosis were randomized to receive a 3- or 4-month moxifloxacin regimen (moxifloxacin [M], isoniazid [H], rifampicin [R], pyrazinamide [Z], ethambutol [E]) or the control regimen (RHZE thrice weekly). Bacteriological assessments were done at 15, 30, 45, and 60 days of treatment. Because all patients in the moxifloxacin groups received 2 months of daily RHZEM, they were grouped together for analysis. Statistical methods included χ^2 test and logistic regression analysis.

Results. Sputum culture conversion was analyzed in 780 (616 in the moxifloxacin group and 164 in the control group) of 801 enrolled patients. Ninety-five percent of 590 patients in the moxifloxacin group and 81% of 151 patients in the control group had negative sputum cultures at month 2 ($P < .001$). The control regimen, age (≥35 years), initial sputum culture grade (2+ or 3+), and male sex were significantly associated with higher odds of positive sputum cultures at 2 months.

Conclusions. A 5-drug daily regimen with moxifloxacin results in significantly higher sputum culture conversion in the first 2 months compared with a thrice-weekly, 4-drug regimen in patients with newly diagnosed sputum-positive pulmonary tuberculosis.

Keywords. tuberculosis; culture conversion; sputum conversion; moxifloxacin; intensive phase.

Shortening tuberculosis treatment duration is a priority of national control programs and researchers. The fluoroquinolone group of drugs has shown therapeutic potential in the treatment of tuberculosis [1], and we showed that 4- or 5-month regimens in which ofloxacin was substituted for ethambutol achieved high cure rates at the end of treatment and low relapse rates during 24 months of follow-up [2]. Among the newer generation of quinolones, moxifloxacin has bactericidal activity similar to that of isoniazid against multiplying *Mycobacterium tuberculosis* both in vitro and in a murine model [3, 4]. The potential to shorten the duration of therapy by at least 2 months has also been shown in a

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murine model that used a rifampicin/moxifloxacin/pyrazinamide-based regimen [5, 6]. In two 8-week studies, moxifloxacin caused earlier sputum culture conversion by a median duration of 27 and 35 days [7, 8].

An interim analysis of an ongoing open-label randomized controlled clinical trial being conducted in Chennai and Madurai, south India, to assess the efficacy and safety of regimens of moxifloxacin of 3–4 months' duration allowed us to compare rates of sputum culture conversion during the first 2 months of treatment between moxifloxacin and the control regimen (6-month thrice-weekly regimen used in the Indian Revised National Tuberculosis Control Programme [RNTCP]) and identify factors influencing sputum culture positivity at 2 months.

METHODS

Study Participants

The National Institute for Research in Tuberculosis (NIRT) Scientific Advisory Committee and the Institutional Ethics Committee approved the trial, which is registered with the Clinical Trial Registry of India (CTRI 2008/091/000024). All study participants provided written informed consent.

Patient recruitment commenced in May 2007. We screened patients with respiratory symptoms to identify those with newly diagnosed sputum smear–positive pulmonary tuberculosis. We recruited those who were at least 18 years old and lived near our centers, were willing to undergo all investigations and attend the health center daily for supervised outpatient treatment, and permitted home visits by center staff. We excluded patients who were pregnant or lactating, had comorbidities (severe hypertension, diabetes mellitus, epilepsy, serious forms of extrapulmonary tuberculosis, or human immunodeficiency virus [HIV] infection), had received treatment for tuberculosis exceeding 30 days, or weighed <30 kg.

Pretreatment Investigations

Initial screening included 4 sputum specimens (2 spot and 2 overnight collections) for microscopy and culture. Smears were prepared from unprocessed sputum, stained with auramine rhodamine, and read using fluorescence microscopy. Sputum was decontaminated and concentrated prior to culture for mycobacteria by the modified Petroff method [9]. Smears and cultures were graded as previously described by the NIRT laboratory [10]. Positive cultures were identified as *M. tuberculosis* by standard methods [11, 12]. Drug susceptibility testing (DST) was performed on Lowenstein–Jensen medium by the minimum inhibitory concentration method for isoniazid, rifampicin, ethambutol, and ofloxacin based on World Health Organization recommendations [11–13]. The definitions of drug resistance for isoniazid, rifampicin, and ethambutol were the same as used in previous studies [14, 15]; for ofloxacin, drug resistance was defined as growth on 8 mg/L of the media [16]. Because we used only solid media for culture, DST for moxifloxacin was not performed and we used resistance to ofloxacin as a surrogate. In addition, the following tests were done: posterior–anterior chest radiograph; electrocardiograph (EKG); urine examination for albumin, glucose, bile salts, and acetyl isoniazid and rifampicin; total and differential leukocyte counts; hemoglobin estimation; total erythrocyte count; platelet count; liver function tests (serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase); renal function tests (blood urea and serum creatinine); serum uric acid; random blood glucose; and enzyme-linked immunosorbent assay for HIV antibodies.

Follow-up

A physician examined the patients every month and recorded the clinical response, adherence to treatment, and occurrence of adverse drug reactions. Sputum was examined every month by microscopy and culture; 3 specimens (2 overnight and 1 spot) during the treatment phase and 2 specimens (1 overnight and 1 spot) during the follow-up phase. In addition, 2 specimens (1 overnight and 1 spot) were examined on day 15 (week 2) and day 45 (week 6). One positive sputum culture was tested each month for susceptibility to isoniazid, rifampicin, ethambutol, and ofloxacin. Bacteriological examinations were carried out in a blinded fashion and technicians were unaware of the clinical status of the patient and the regimen. An EKG, hemogram, hepatic and renal function tests, and random blood glucose tests were repeated every month. At the end of the intensive phase of treatment, a chest radiograph was obtained. Patients were followed up for 24 months after treatment completion.

Regimens and Randomization

Eligible patients were randomly allocated to 1 of the following 4 test regimens or a control regimen (R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol; M = moxifloxacin):

1. RHZEM daily for 3 months;
2. RHZEM daily for 2 months followed by RHM daily for 2 months;
3. RHZEM daily for 2 months followed by RHM thrice weekly for 2 months;
4. RHZEM daily for 2 months followed by RHEM thrice weekly for 2 months; or
5. RHZE thrice weekly for 2 months followed by RH thrice weekly for 4 months (control regimen).

Regimen allocation was stratified based on sputum smear grading of the penultimate home sputum specimen (first stratum, 0 or 1+; second stratum, 2+ or 3+), chest radiographic involvement (first stratum, ≤2 zones; second stratum, >2 zones) and duration of previous antituberculosis treatment (first stratum, 0–14 days; second stratum, 15–30 days). Restricted random

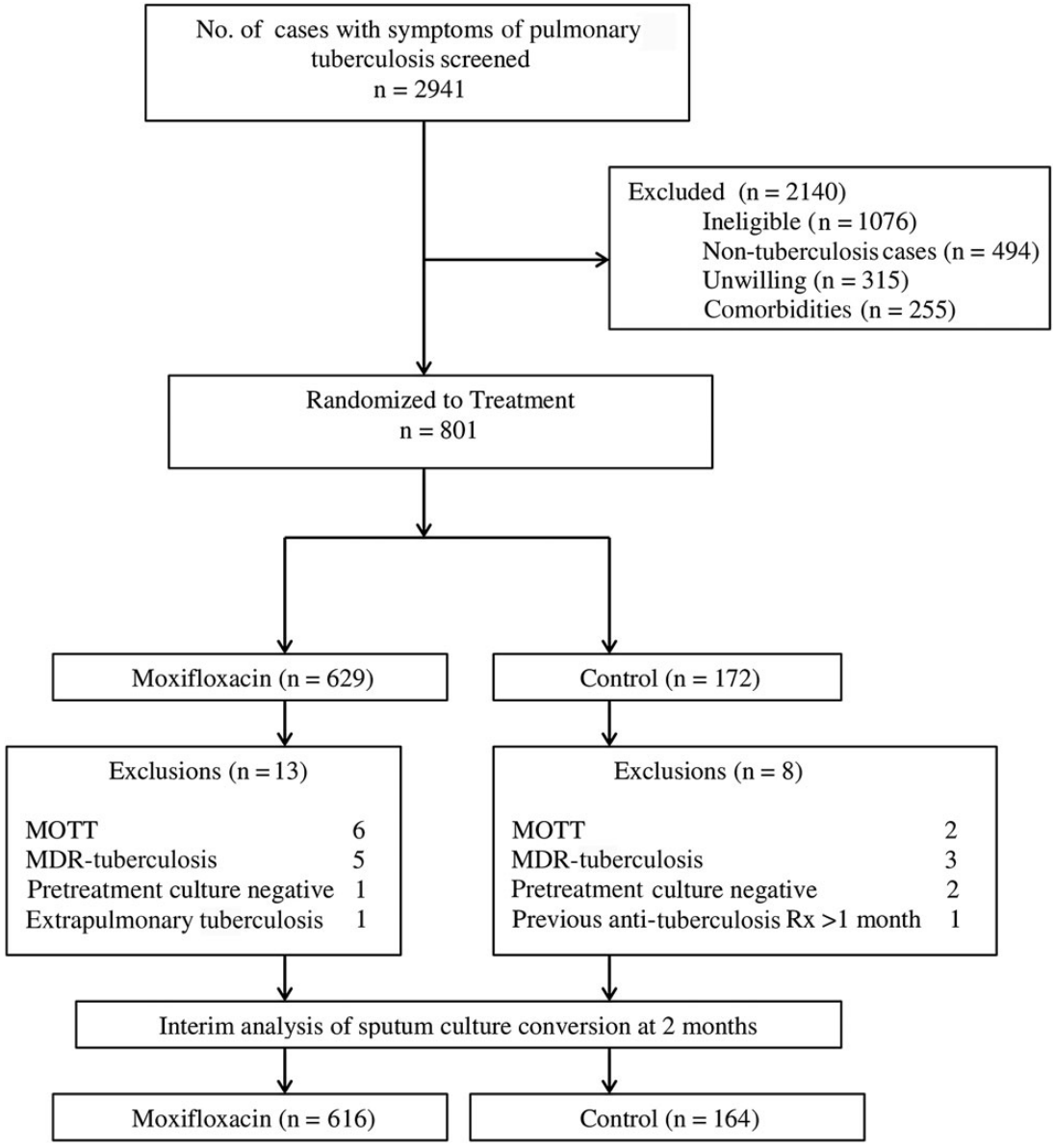

Figure 1. Flow diagram of patients from screening to analysis. Abbreviations: MDR-tuberculosis, multidrug-resistant tuberculosis; MOTT, mycobacteria other than tuberculosis; Rx, treatment.

allocation sequences generated using random number tables, separately for the 6 strata, were used to assign the regimens.

We used the following doses of antituberculosis drugs: rifampicin 450 mg (<60 kg body weight) or 600 mg (≥60 kg body weight); isoniazid 300 mg (daily) or 600 mg (thrice weekly); pyrazinamide 1500 mg; ethambutol 800 mg (daily) or 1200 mg (thrice weekly); and moxifloxacin 400 mg (fixed dose). During the daily phase, treatment was under direct observation on 5 of 7 days of the week, whereas 2 doses were self-administered. All thrice-weekly phase doses were directly observed. Patients who missed treatment visits were visited at home and motivated to attend the clinic for treatment. Missed doses were compensated.

Analysis

This interim analysis is restricted to the results of sputum culture conversion during the first 2 months of treatment examining proportion of patients with 2 negative sputum cultures on day 15, day 30, day 45, and day 60. Because all patients allocated to the 4 moxifloxacin regimens received the same daily treatment (RHZEM) for the first 2 months, we combined the results of these regimens and compared them with the control regimen.

Table 1. Baseline Characteristics of 780 Patients With Sputum-Positive Pulmonary Tuberculosis Included in the Interim Analysis

	Regimen						
	Moxifloxacin (n = 616)		Control (n = 164)			Total Patients	
Characteristics	No.	%	No.	%	*P* Value	No.	%
Sex							
Male	455	74	127	77	.350	582	75
Female	161	26	37	23		198	25
Age, y							
<35	293	48	79	48	.802	372	48
≥35	323	52	85	52		408	52
Body weight, kg							
<42	288	47	75	46	.816	363	46
≥42	328	53	89	54		417	53
Sputum smear grade[a]							
1+	95	15	18	11	.151	113	14
2+	303	49	83	51		386	49
3+	218	35	63	38		281	36
Sputum[b] culture grade							
≤1+	30	5	4	2	.315	34	4
2+	105	17	38	23		143	18
3+	481	78	122	74		603	77
Chest radiograph							
≤2 zones[c]	135	22	37	23	.859	172	22
>2 zones	481	78	127	77		608	78
Cavity present	224	36	68	41	.230	292	37
No cavity	392	64	96	59		488	63
Sputum drug sensitivity profile							
Susceptible to H, R, E, O	535	87	139	85	.371	674	86
Resistant to							
H	44	7	13	8		57	7
R	3	<1	1	<1		4	
E	1	<1	0	0		1	
O	30	5	11	7		41	5
H, E	1	<1	0	0		1	
H, O	2	<1	0	0		2	

Abbreviations: E, ethambutol; H, isoniazid; O, ofloxacin; R, rifampicin.

[a] Sputum smear grading: <6 bacilli per high-powered field (HPF) (1+), 6–100 bacilli/HPF (2+), >100 bacilli/HPF or large clumps (3+).

[b] Sputum culture grading: actual number up to 19 colonies; 20–100 colonies (1+); >100 colonies (2+); and confluent growth (3+).

[c] Total of 6 zones, 3 in each lung.

We included the results of the first 2 specimens only, as we collected only 2 sputum specimens at days 15 and 45.

Statistics

We used a modified intention-to-treat analysis and excluded patients whose baseline sputum cultures were negative, positive for mycobacteria other than *M. tuberculosis* (MOTT), or harbored multidrug resistant organisms from the analysis (Figure 1). We compared the proportions of patients with sputum culture conversion at days 15, 30, 45, and 60 of treatment in the moxifloxacin group and the control group using χ^2 test, and calculated *P* values with 95% confidence intervals (CIs). Logistic regression was done by both adjusted and unadjusted methods with treatment allocation and baseline characteristics selected by the investigators as covariates. Sputum culture positivity at 2 months of treatment was the dependent variable. We used the "ENTER" method for data entry and the Hosmer-Lemeshow test to identify goodness of fit. All analyses were done using SPSS version 20.0.

Table 2. Sputum Culture Conversion During First 2 Months of Treatment (Moxifloxacin Regimens 616, Control Regimen 164)

Days of Treatment	Regimen	Patients Examined	Sputum Culture Negative		*P* Value	Difference in Proportion (95% CI)
			No.	%		
15	Moxifloxacin	605	84	14	.03	0.064 (.006–.107)
	Control	160	12	8		
30	Moxifloxacin	602	295	49	<.001	0.220 (.136–.295)
	Control	159	43	27		
45	Moxifloxacin	581	485	84	<.001	0.231 (.148–.317)
	Control	144	87	60		
60	Moxifloxacin	590	563	95	<.001	0.146 (.088–.218)
	Control	151	122	81		

Missing data: day 15 (n = 15: death 1, default 7, sputum not collected 7); day 30 (n = 19: death 2, default 11, sputum not collected 6); day 45 (n = 55: death 3, default 12, sputum not collected 40); day 60 (n = 39: death 4, default 14, sputum not collected 21).

Abbreviation: CI, confidence interval.

RESULTS

We screened 2941 individuals to enroll 801 patients in the study (629 to moxifloxacin regimens and 172 to the control regimen). Thirteen (2.1%) and 8 (4.7%) patients, respectively, were excluded from analysis for the following reasons: 8 had sputum cultures positive for MOTT; 3 had no initial positive sputum cultures; 1 had received previous antituberculosis treatment exceeding 1 month; 8 had multidrug-resistant tuberculosis and 1 had concomitant extrapulmonary tuberculosis. The results of sputum culture conversion in 780 patients (616 in the moxifloxacin group and 164 in the control group) are presented in this interim analysis (Figure 1). Patient enrollment and follow-up are ongoing.

Baseline Characteristics

The baseline demographic and clinical characteristics were similar between the 2 treatment groups (Table 1).

Sputum Culture Conversion

The proportion of patients with negative sputum cultures for 2 sputum specimens on days 15, 30, 45, and 60 in the 2 treatment groups is shown in Table 2. At the end of 2 months of treatment, 563 of 590 (95%) patients in the moxifloxacin group and 122 of 151 (81%) patients in the control group had negative sputum cultures (difference in proportion, 0.146; 95% CI, .088–.218; $P < .001$). The proportion of patients with negative sputum cultures was significantly higher in the moxifloxacin group at all time points.

At 2 months, 56 of 741 patients with available sputum culture results had positive cultures. Patients treated with the control regimen, men, and those aged ≥35 years had significantly higher odds of having positive sputum cultures at 2 months of treatment, both in the unadjusted and adjusted logistic regression analysis (Table 3). Patients with initial sputum culture grading of 2+ or 3+ were more likely to have positive culture by the second month of treatment compared to those with 1+ culture grading (8% vs 0%).

Drug-Related Adverse Events

Arthralgia was significantly higher in the moxifloxacin group (25%) compared with the control group (4%). Skin rash with or without pruritis occurred in 5% and 4% of patients, respectively, in the moxifloxacin and control groups. Five patients in the moxifloxacin group showed prolongation of the QTc interval above the protocol-defined upper limit of 450 ms, and moxifloxacin was temporarily withheld and later reintroduced. No patient developed arrhythmias. One patient in the control group also had QTc prolongation. Two percent and 1% of patients in the moxifloxacin and control groups, respectively, developed hepatitis. Six patients developed seizures, 4 in the moxifloxacin group and 2 in the control group.

DISCUSSION

An interim analysis of our ongoing trial has shown that addition of moxifloxacin to the 4-drug regimen of RHZE to treat patients with newly diagnosed sputum-positive pulmonary tuberculosis shortened the time to culture conversion compared with the control regimen. The kinetics of conversion clearly demonstrated that it started as early as day 15 and continued through the second month (Table 2).

The very high sputum culture negativity (95%) observed in our study at 2 months in the moxifloxacin group is similar to the results of a report from Taiwan in which moxifloxacin added to the standard daily antituberculosis regimen resulted in a higher proportion of patients with negative cultures at 6

Table 3. Predictors of Positivity of Sputum Cultures at the End of 2 Months of Treatment in Patients in the Moxifloxacin and Control Groups (n = 741)

Independent Variable	Patients Examined (n = 741)	Culture Positive No	Culture Positive %	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Regimen							
Moxifloxacin	590	27	5	Ref		Ref	
Control	151	29	19	5.31 (3.03–9.29)	.001	5.52 (3.10–9.82)	.001
Sex							
Female	192	6	3	Ref		Ref	
Male	549	50	9	3.76 (1.48–9.57)	.005	2.90 (1.06–7.95)	.038
Age, y							
<35	396	20	5	Ref		Ref	
≥35	345	36	10	2.34 (1.32–4.16)	.004	1.98 (1.06–3.67)	.031
Body weight, kg							
≥42	401	32	8	Ref		Ref	
<42	340	24	7	0.81 (.47–1.41)	.454	1.14 (.63–2.08)	.666
Initial sputum culture grade[a]							
1+	33	0	0	Ref		Ref	
2+ or 3+	708	56	8	[a]		[a]	
Initial sputum drug susceptibility							
Susceptible	640	44	7	Ref		Ref	
Resistant	101	12	12	1.80 (.91–3.53)	.089	1.70 (.82–3.50)	.152
Chest cavity radiograph							
Absent	462	37	8	Ref		Ref	
Present	279	19	7	0.84 (.47–1.49)	.554	0.74 (.41–1.36)	.331

Logistic regression models were fit with positive sputum cultures at the end of 2 months of treatment as the outcome of interest

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; Ref, reference.

[a] Difference between 1+ and 2+ or 3+ highly significant: *P* value not available because the 1+ group had 0.

weeks (82% vs 61%; *P* = .011) but not at 8 weeks compared with the control group (92% vs 83%; *P* = .15) [7]. In a study in Brazil [8], when ethambutol was substituted by moxifloxacin in the standard 4-drug daily regimen, it resulted in higher culture negativity at 8 weeks in the moxifloxacin regimen (80% vs 63%), but lower than observed in the present study. However, in the Brazilian study, moxifloxacin was given only for 5 days per week. In contrast, studies by the Tuberculosis Trials Consortium showed no significant difference in the 8-week culture negativity when moxifloxacin replaced ethambutol or isoniazid [17, 18]. Two-month cultures were negative in 71% of patients (99 of 139) treated with moxifloxacin vs 71% (98 of 138) of those treated with ethambutol (*P* = .97); 8-week cultures were negative in 54.9% (90 of 164) and 60.4% (99 of 164) of patients treated with the isoniazid and moxifloxacin regimens, respectively (*P* = .37) [17, 18].

In the present study, patients in the moxifloxacin group were less likely to have positive sputum cultures at 2 months (adjusted logistic regression analysis). Older age (≥35 years) was associated with positive sputum cultures at 2 months, as was shown in a previous study where age >31 years was significantly associated with lower second-month sputum culture conversion [17]. Men were more likely to have positive sputum cultures at 2 months, unlike in earlier studies [8, 17, 18]. In our study, culture conversion was not influenced by cavitary disease reported by other investigators [18].

The regimens were generally well tolerated, except for arthralgia, which occurred in a quarter of the patients receiving the moxifloxacin regimen compared with 4% of the patients receiving the control regimen. However, arthralgia was mild, easily manageable with symptomatic measures, and did not necessitate change of antituberculosis treatment. We surmise this is due to the addition of moxifloxacin to a daily regimen that already contains pyrazinamide, a drug known for its potential to induce arthralgia. Even though 5 patients in the moxifloxacin group had QTc prolongation >450 ms, none developed cardiac arrhythmias.

In comparing the results at 2 months, it is important to consider the role of the rhythm of the regimens. In the present

study, culture conversion was higher in the daily-treated moxifloxacin group than in the thrice-weekly control group. In another study, a daily RHZE regimen resulted in higher culture conversion at 2 months compared with a similar thrice-weekly regimen (85% vs 77%) [19]. However, we previously showed a higher second-month culture conversion with a thrice-weekly moxifloxacin (88% vs 78%) regimen than with a thrice-weekly RHZE regimen [20]. It is likely that both the drug and the rhythm influence culture.

The most significant finding of this interim analysis is the higher conversion rate seen at 2 months in the moxifloxacin group. There has been considerable debate on the value of the 2-month culture conversion as a possible predictor of treatment success or relapse and as an important factor in the construction of an antituberculosis regimen. At 2 months, with the elimination of the bulk of the bacterial population, a less intensive maintenance phase can be used to achieve sterilization, which is key to prevention of recurrence. Although a good correlation between second-month culture results and relapse rates has been suggested [21], other studies have indicated that it may not be a good predictor of long-term success of a regimen. In previous studies we showed that even when the second-month culture-negative rates were as high as 91% and 92%–98%, tuberculosis recurred in 20% and 8%–13% of patients, respectively [2, 22]. A recent report that analyzed 12 randomized trials involving 6974 participants using 49 regimens in the 1970s and 1980s concluded that it was a poor surrogate marker in East Africa but performed better in Hong Kong [23]. A systematic review and meta-analysis also found that the second-month sputum culture conversion had low sensitivity and modest specificity for predicting treatment failure and relapse [24].

Our study has shown that supplementing the RHZE regimen with moxifloxacin can significantly hasten sputum culture conversion. This observation has important public health implications, as rapid conversion of sputum positivity significantly interrupts transmission and reduces exposure risk to the community. It also allows the design of a less intensive continuation phase using possibly fewer drugs and shorter durations.

This study is not without its limitations. We did not document the kinetics of sputum conversion more closely, as we did not examine sputum at weekly or more frequent intervals as in previous studies. It is likely that such an examination would have identified a possible earlier conversion with moxifloxacin. We did not include a direct comparison of daily regimens devoid of moxifloxacin but used the standard thrice-weekly RNTCP regimen instead. We recognize that the 2 groups were not truly "randomized" as the moxifloxacin group is a composite of 4 different patient groups, and this limits the scope of the analysis. We were also limited by the lack of DST techniques to measure moxifloxacin resistance and used resistance to ofloxacin as a proxy indicator. A recent study [25] that demonstrated the concordance between ofloxacin and moxifloxacin resistance, however, justifies our use of ofloxacin resistance as a surrogate.

CONCLUSIONS

Our results have shown that addition of moxifloxacin to a 4-drug daily regimen for the treatment of newly diagnosed smear-positive pulmonary tuberculosis significantly improves conversion of sputum positivity at 2 months. Our results suggest that supplementing regimens with moxifloxacin instead of using it to replace component drugs may be important in achieving higher conversion rates. The rapid clearance of sputum shown in this study has public health implications, as transmission will be interrupted earlier in the course of treatment and holds the promise of shorter regimens. Such shorter short-course regimens could be used to design better tuberculosis control programs that are not only less costly but also enhance patient compliance.

However, in assessing the benefits of moxifloxacin-containing regimens, the risk of development of resistance due to long periods of exposure and the issue of tolerance to the drug should also be considered. A recent meta-regression model of second-month culture results for moxifloxacin-containing regimens suggests that relapse rates similar to standard therapy would be achieved only if moxifloxacin is administered for ≥5 months [26]. The results of the planned follow-up of patients in the present study will undoubtedly help in validating this model. The potential development of resistance can perhaps be prevented by implementing stringent regulations restricting use of moxifloxacin. Although the unusually high frequency of arthralgia in this study is disturbing, other studies, including a recent study of ours where its frequency was only 3% (thrice-weekly regimen) [20], suggest that moxifloxacin is generally well tolerated.

Clearly, additional studies that document long-term efficacy of moxifloxacin-containing regimens (including relapse and failure) and others that address cost-benefit issues are required not only to confirm these results but to help in realizing the promise of these regimens. Results of long-term follow-up (beyond 2 months and up to 2 years) of patients enrolled in this study, when available, will likely provide important information about relapse and failure on these regimens.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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